
Visual activity regulates neural progenitor cells in developing xenopus CNS through musashi1.

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Public Summary:

During development stem cells give rise to nerve cells in the central nervous system. During the first stages of development, stem cells divide each generating two identical daughter stem cells. This process (proliferation) serves to increase the pool of stem cells. In later stages, stem cell divisions generates two different types of cells: a daughter stem cell plus a cell that changes into a mature, functioning nerve cell (called differentiation). Moreover, once the nervous system approaches the final stages of development, all divisions give rise to nerve cells, leaving only a few stem cells behind. So how is the switch from mainly stem cell proliferation to mainly nerve cell differentiation controlled in the developing brain? It is known that in adult brains, brain activity helps new nerve cells form and existing ones survive. However, no one had looked at the connection between brain activity and nerve cell formation in the developing brain. To look for a possible link, Cline turned to the frog *Xenopus laevis*. In tadpoles stem cells in the visual system—the part of the brain that receives and interprets signals from the eyes—continue to proliferate for several days even as brain circuits are starting to form and become functional. The researchers wanted to ask whether the activity by the newly formed circuits had any effect on stem cell proliferation and nerve cell differentiation. We determined that the amount of stem cell proliferation in the visual system decreases as the visual circuits are laid out and become active (from about days 7 to 13 in a tadpole's life). However, when the activity was shut off in the visual system by keeping some of the tadpoles in darkness for two days, cell proliferation increased and nerve cell differentiation decreased. These observations suggest that brain activity regulates both stem cell proliferation and nerve cell differentiation, but in opposite ways. As circuits are laid out during development, their activity influences the fate of cells generated through stem cell division, making them stop dividing and mature into nerve cells. We have found that a key reason why proliferation slows down during development is that brain activity turns it off. During visual system development, as stem cell proliferation decreases, they found that the amount of a protein called Musashi1, which is produced by stem cells, also decreases. On the other hand, the tadpoles kept in the dark for two days, whose visual system was not active, had an increase in both stem cell proliferation and an increase in Musashi1 protein levels in the stem cells. In a series of experiments, we either shut down or boosted the production of musashi1 in the tadpoles' stem cells. We showed that in the absence of Musashi1 stem cell proliferation slows down. On the other hand, boosting the amounts of Musashi1 increases stem cell proliferation, even in the later stages of development. The findings suggest that Musashi1 protein might be used as a way of expanding the stem cell pool in developing brains.

Scientific Abstract:

Regulation of progenitor cell fate determines the numbers of neurons in the developing brain. While proliferation of neural progenitors predominates during early central nervous system (CNS) development, progenitor cell fate shifts toward differentiation as CNS circuits develop, suggesting that signals from developing circuits may regulate proliferation and differentiation. We tested whether activity regulates neurogenesis in vivo in the developing visual system of *Xenopus* tadpoles. Both cell proliferation and the number of musashi1-immunoreactive progenitors in the optic tectum decrease as visual system connections become stronger. Visual deprivation for 2 days increased proliferation of musashi1-immunoreactive radial glial progenitors, while visual experience increased neuronal differentiation. Morpholino-mediated knockdown and overexpression of musashi1 indicate that musashi1 is necessary and sufficient for neural progenitor proliferation in the CNS. These data demonstrate a mechanism by which increased brain activity in developing circuits decreases cell proliferation and increases neuronal differentiation through the downregulation of musashi1 in response to circuit activity.